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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/019,586 | 12/20/2001 | Vanessa Chisholm | P1746R1 | 1705 |

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| EXAMINER | |
|---|---|
| AKHAVAN, RAMIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicants 09/07/04

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/019,586 | CHISHOLM ET AL. | |
| | Examiner | Art Unit | |
| | Ramin (Ray) Akhavan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,8-34,36-58,102 and 103* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-34,36-58,102 and 103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Acknowledgment is made of an amendment filed, 06/16/2004, canceling claims 59-101, adding new claims 102-103. The claims pending and under consideration are 1-6, 8-34, 36-58 and 102-103. Any objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to applicant's arguments will be included in the body of any objections/rejections maintained. As new grounds of rejection are set forth, this action is NON-FINAL.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. **Claims 1-6, 8-34, 36-58 and 102-103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Base claim 1 as well as dependent claims recite the term "gene", which confers ambiguity and vagueness. A gene encompasses intervening and untranslated regions. Therefore, as written, it is unclear whether the claims are to be interpreted as encompassing merely the sequence encoding the GFP protein, for example, or encompassing all regions of the particular gene. As a result of this ambiguity the claims' metes and bounds are indefinite. It would be remedial to replace the term "gene" with the phrase such as, "nucleic acid encoding GFP".

Claim 49 recites the term, "expression" when referring to such expression being indicative of the cell also expressing the desired product. It is unclear expression of what is actually indicative.

In addition, with respect to claim 102, there is an internal conflict with respect to the encompassed limitations. A GFP gene cannot be a GFP-fusion gene. If the former is to be interpreted to mean a gene encoding GFP then it cannot be the same as a GFP-fusion gene, which necessarily indicates a gene encoding GFP as well as an additional heterologous protein. Due this ambiguity it is unclear how the claim's metes and bound are to be interpreted. It would be remedial to use more particular or definite language so as to reflect that a gene encoding GFP is fused to an additional gene encoding a different protein, thus constituting a GFP-fusion gene. As written, it is not clear that a GFP gene encompasses a fusion with a heterologous protein, notwithstanding, what is disclosed in the specification.

***Claim Rejections - 35 USC § 103***

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**2. Claims 1-6, 8-9, 39-44 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (US 6,235,967; see whole document; hereinafter the '967 patent) as applied to or further in view of Chishima et al. (Cancer Res. 1997; 57:2042-47; previously cited).**

The claims are drawn to a polynucleotide comprising an amplifiable gene, a green fluorescent protein (GFP) and a selected sequence encoding a desired product (i.e. target gene), where the target gene is operably linked to either the amplifiable gene or to GFP and to a promoter. The limitation, operably linked is interpreted as broadly as reasonable, to include the interpretation that nucleic acids are linked in some fashion so as to confer a functional objective (e.g. amplification or propagation of a vector in bacteria). Furthermore, the claims are directed to the amplifiable gene encoding DHFR and the GFP is further limited to mutant GFP – S65T. The invention is further directed to cells and a kit comprising the polynucleotide with the aforementioned characteristics. In addition, the limitation for a kit is interpreted as broadly as reasonable to mean any container comprising the polynucleotides of the invention.

The '967 patent teaches a polynucleotide where GFP is fused to a selected sequence (e.g. methioninase or T antigen) and operably linked to a promoter. (e.g. Abstract; Fig. 1a). Furthermore, GFP can be of a higher fluorescence mutated (i.e. S65T) variety. (e.g. col. 3, l. 26). In addition, various cell types can be transfected with the polynucleotide, including methotrexate

selected CHO cells. (e.g. col. 3, line 63; col. 6, ll. 27-37). Furthermore, the '967 indicates using a DHFR-GFP dicistronic vector (e.g. col. 6, Example 1; showing GFP-S65T mobilization into pED-mtx$^r$) and explicitly teaches that such vector systems can be used to express proteins in mammalian cells. (e.g. col. 9, ll. 40-45). In addition, the polynucleotides would necessarily be contained in a container (e.g. eppendorf tubes), which constitutes a kit. The '967 patent doesn't expressly provide a construct where a target gene is operably linked to either a gene encoding GFP or a gene encoding an amplifiable selectable marker, where the construct comprises both genes regardless.

However, in essence, the '967 patent all but reduces to practice what is missing. For example, a GFP-target fusion is taught with a selection marker. (e.g. Fig. 1a). Furthermore, the '967 patent teaches that a dicistronic vector comprising both a fluorescence encoding gene (i.e. GFP) and an amplifiable selectable marker (i.e. DHFR) can be used. (e.g. col. 9, ll. 40-45). In addition, the '967 patent teaches that said polynucleotides can be used for production of a fusion protein (e.g. GFP-T antigen). (e.g. col. 9, ll. 50-51). Therefore, the '967 patent provides the motivation to construct a vector comprising a gene encoding a fluorescence marker, an amplifiable selectable marker and a target protein.

In addition, Chishima et al. teach an expression construct where a GFP gene (S65T) is mobilized into a dicistronic expression vector comprising an amplifiable gene (i.e. DHFR) and a gene expressing a desired product. (Chishima, at 2042, col. 2, ¶3, referring to the pED-mtx$^r$ construct described in, Kaufman et al. Nucleic Acids Research. 1991; 19(16):4485-90) (Note: this second reference is only being cited to provide information with regard to intrinsic properties of the pED-mtx$^r$ expression construct not as additional art, See MPEP § 2131.01). Kaufman et

al. teach that the pED-mtx$^r$ construct contains a gene encoding a desired product operably linked to a promoter (i.e. B-lactamase gene, Kaufman, at 4487, Fig. 1). Chishima et al. further teach that the construct replicates in CHO cells. (Chishima, at 2042, col. 2, ¶4).

Therefore, it would have been well within the knowledge of one of ordinary skill to construct the expression vector to produce the GFP fusion proteins as contemplated by the '967 patent. The ordinary skilled artisan, seeking to develop a construct for expressing proteins that can be easily be monitored via fluorescence and that can be selected for in mammalian cells via amplifiable markers such as DHFR, would have been motivated to incorporate the teachings of the '967 patent or Chishima et al. to construct a expression construct comprising GFP, a selected sequence and DHFR, operably linked to a promoter. It would have been obvious for the ordinary skilled artisan to so construct an expression vector and transfect mammalian cells to express the desired fusion proteins. Furthermore, given the teachings of the cited references and the level of skill of the ordinary skilled artisan at the time of applicants' invention, it must be considered that said artisan would have had a reasonable expectation of success in practicing the claimed invention.

3. **Claims 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (US 6,235,967; see whole document; hereinafter the '967 patent) or Chishima et al. (Cancer Res. 1997; 57:2042-47; previously cited), and further in view of Moir and Mao (Bioprocess Technol. 1990; 9:67-94;See whole document; previously cited) or Lubiniecki and Lupker (Biologicals. 1994, 22(2): 161-9;See whole document; previously cited).**

The '967 patent nor Chishima et al. do not explicitly indicate that proteins expressed can be recovered or recovered from culture.

Moir and Mao teach that proteins of interest can be produced and targeted to different compartment of cells within which they are produced or secreted into the culture medium using secretory pathways of yeast and mammalian cells. (See e.g. p. 67, ¶1). Moir and Mao explicitly state that protein products from exogenously added genes on recombinant vectors can be targeted to the culture medium for production (i.e. recovery) of industrially important proteins. (Id., ¶¶ 1-3). Furthermore, Lubiniecki and Lupker teach that recombinant proteins produced in an animal cell culture system can be purified using chromatography techniques known in the art to medicinal quality. (p. 167, ¶ 3).

The ordinary skilled artisan seeking to produce proteins for biotechnology or pharmaceutical applications in cell culture systems would have been motivated to combine the teachings of the '967 patent or Chishima et al. – an expression system designed to express proteins of interest in addition to sorting via fluorescence – with the teachings of Moir and Moi or Lubiniecki and Lupker – using cell culture systems combined with standard chromatography techniques to purify (i.e. recover) proteins of interest, with the added benefit of FACS sorting. The whole point of Meng et al. is to select cells that are producing proteins, thus would have been obvious for the ordinary skilled artisan to incorporate the selection/expression system of Meng et al. to express proteins that could then be purified or recovered.

Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of applicant's invention, it must be considered that the skilled artisan would have had a

reasonable expectation of success in making recombinant protein to be recovered from a cell culture system using applicant's selection/expression system.

***Response to Arguments***

Applicants' argument (Remarks, filed 06/16/04, pages 15-16) are centered on Chishima et al. not teaching the claimed limitations as rejected under 35 U.S.C. § 102(b), but are moot in light of the new grounds of rejection made under 35 U.S.C. § 103.

***Conclusion***

A copy of the newly cited art is submitted herewith for applicants' review.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636
September 7, 2004

GERRY LEFFERS
PRIMARY EXAMINER